PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

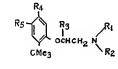
Ortho-Tertiary-Butyl Phenolethers

We, THE CROOKES LABORATORIES LIMITED, a British Company, of Gorst Road, Park Royal, London, N.W.10, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

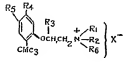
This invention relates to new derivatives of o-tert. butyl phenols and more particularly to the preparation of basic ethers of o-tert. butyl phenols, their salts and quaternary ammonium compounds derived from these bases.

These new compounds possess pharmacological activities in warm blooded animals as central nervous depressants, analgesics, long acting local anaesthetics and as blocking agents in the sympathetic nervous system.

These compounds are basic ethers of o-tert. butyl phenol (I) and their quaternary ammonium derivatives (II) and may be represented by the general formulae shown below:



I



II

where R_1 and R_2 may be the same or different groups chosen from hydrogen, or an alkyl group of not more than four carbon atoms, or phenethyl, or R_1 and R_2 may be joined as part of a heterocyclic ring, e.g., piperidine; R_3 may be hydrogen or an alkyl group of not more than four carbon atoms, R_4 and R_5 may be hydrogen, an alkyl group of not more than four carbon atoms, alkyloxy, hydroxy, amino or acylamino groups; R_6 is the group introduced by quaternization of I to give II and is an alkyl group of not more than four carbon atoms; X is the anion associated with the quaternary salt (II) and may be chloride, bromide, iodide, p-toluenesulphonate, salicylate or isethionate. Alternatively, R_6 may be hydrogen when II then no longer represents a quaternary ammonium compound but represents the simple acid addition salts of the tertiary base I and in this case X may be the anion of a simple inorganic or organic acid such as hydrochloric, tartaric or citric acid.

Compounds of type I, may be prepared from an o-tert. butyl phenol, carrying substituents R_4 and/or R_5 as described above, by several methods. Firstly, the phenol may be reacted with β-dialkylamino alkyl halide in the presence of alkali-metal alcoholates or carbonates. Other suitable syntheses may be employed wherein the above described o-tert. butyl phenol is first converted to the corresponding o-tert, butyl phenyl-alkyl ether carrying a reactive substituent in the β-position of the alkyl group, this reactive substituent being subsequently replaced by a mono- or dialkylamino group. Thus the substituted o-tert. butyl phenol may be reacted with a reactive ester of an alkylene chlorohydrin or bromohydrin, e.g., a p-toluene-sulphonyl ester, and the halogen atom of the resulting β-haloalkoxy-o-tert. butyl benzene exchanged for a mono- or dialkylamino group. Alternatively, the o-tert. butyl phenol may be reacted

[*Price 4s. 6d.*]

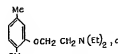
with an alkylene chlorohydrin or bromohydrin, in the presence of alkali-metal alcoholates or carbonates and the resulting β-hydroxy alkoxy-o-tert. butyl benzene derivative converted to an ester such as the p-toluene sulphonate; this ester may then be reacted with a primary or secondary amine to give the β-alkylamino- or β-dialkylamino alkoxy-o-tert. butyl benzene. Also, an appropriately substituted o-tert. butyl phenol may be converted to an o-cyanoalkoxy-tert. butyl benzene by reaction with chloroacetonitrile or a substituted chloroacetonitrile and this may be reduced to the corresponding o-β-amino alkoxy-tert. butyl benzene after which the primary amino group may be substituted with one or two alkyl groups.

The new basic ethers (I) are liquids at ordinary temperatures; they may be distilled at low pressure and for the most part form crystalline salts with common inorganic or organic acids to give compounds of type II where R_6 is specifically hydrogen.

Compounds of type I or their simple salts (type II, R_6 is hydrogen) possess pharmacologically different properties from compounds of type II (R_6 is alkyl) and may be described separately.

Basic ethers of type I and their salts (II, R_6=H).

Basic ethers of type I and their salts possess central nervous depressant and analgesic properties. These pharmacological properties were assessed by comparison with the well known drugs pethidine and chloropromazine. Some results for 2-diethylaminoethoxy-4-methyl-t-butylbenzene citrate, formula III, are shown below.



(III)

The acute intraperitoneal toxicity of compound III in mice, expressed as the LD_{50} (i.e., the dose causing 50% of the animals to expire within 5 days), was 382 mg./kg.

Central Nervous System depressant action.

The prolongation of hexobarbitone induced hypnosis caused by compound III, was compared with the similar effect caused by an equivalent fraction of the LD_{50} of chlorpromazine. The potency of compound III as an inhibitor of spontaneous motor activity (the ED_{50} being that fraction of the LD_{50} required to cause 50% inhibition of spontaneous motor activity) of mice, and the percentage inhibition of cocaine-induced hyperactivity of mice, produced by compound III, were compared with the corresponding properties of chlorpromazine. The results are shown in Table I.

TABLE I

	Prolongation of hexobarbitone hypnosis at 1/10th LD_{50}	Inhibition of spontaneous motor activity. ED_{50} (v. sup.)	Inhibition of cocaine induced hyperactivity at 1/20th LD_{50}
Compound III	237%	1/90th LD_{50}	65%
Chlorpromazine	263%	1/91st LD_{50}	76%

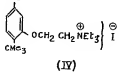
Analgesia.

The degree of analgesia relative to pethidine was determined by the mouse-clip test, as described by Bianci, (Brit. J. Pharmacology and Chemotherapy, 1956, *11*, 104). The relative results are:

	Compound III 1/5th LD_{50}	Pethidine 1/5th LD_{50}
Analgesia	71%	53%

Quaternary ammonium compounds of type II (R_6=alkyl).

These compounds (II, R_6=alkyl) possess long acting local anaesthetic properties and give pharmacological evidence of sympathetic blockade. In the case of the following compound (IV)



(IV)

the pronounced central depressant actions of its unquaternized analogue have been lost; hexobarbitone sleeping times are not affected by the compound (IV) in a dosage of 1/10th LD_{50} by the intraperitoneal route. The compound has no analgesic activity in the clip test but it potentiates the action of pethidine and codeine. The compound (IV) gives a prolonged anaesthesia in tests measuring conduction of impulses in the mouse tail and guinea pigs skin as the following figures show for a dosage of 0.1 ml. of a 1% solution:

	Duration
Conduction anaesthesia	142 hours
Infiltration anaesthesia	260 hours
Surface anaesthesia	Nil.

In high dosage, compound IV gives a curare-like neuromuscular blockade in the chick.

The following examples illustrate the manner of preparing the compounds.

EXAMPLE 1

The Preparation of 2(β-diethylaminoethoxy)-4-methyl-t-butylbenzene.

To a solution of 5 g. of sodium in 400 ccs. of absolute ethanol is added 16.4 g. of 2-t-butyl-5-methylphenol, followed by 19 g. of β-diethylaminoethylchloride hydrochloride. The mixture is boiled under reflux for seven hours, cooled, filtered from salt and the filtrate evaporated to dryness. The residue is dissolved in ether and the solution washed successively with three, fifty-millilitre portions of approximately 4N. hydrochloric acid and once with water. The aqueous washings are made alkaline by addition of 40% sodium hydroxide solution and extracted with ether. The ether solution is washed with water, dried over magnesium sulphate and evaporated to dryness. Distillation of the residue at reduced pressure, afforded 10.8 g. of the required amine, b.p. 114—118°/0.7 mm. The citrate has a melting point of 146—147°, and the picrate, 133—134°.

EXAMPLE 2

2(2-t-Butyl-5-methylphenoxy)ethyl triethylammonium iodide.

A mixture of 3 g. of 2(β-diethylaminoethoxy)4-methyl-t-butylbenzene and 15 ccs. of ethyl iodide is boiled under reflux for two hours. The excess of ethyl iodide is boiled off and the residue is digested with dry ether. The white solid is recrystallised from a mixture of ethanol and ether, and from water, to obtain 1.9 g. of white solid, m.p. 193—194°.

EXAMPLE 3

2-(2-Aminoethoxy)-4-methyl-t-butylbenzene.

Five grams of 2-cyanomethoxy-4-methyl-t-butylbenzene dissolved in 50 ccs. of dry ether is added dropwise during 20 minutes, to a stirred mixture of 2 g. of lithium aluminium hydride and 250 ccs. of dry ether. The mixture is stirred for 2 hours and after adding moist ether to decompose unreacted hydride, 50 ccs. of approximately 2 N. hydrochloric acid solution is added. The hydrochloric acid layer is made strongly alkaline and the product extracted into ether to obtain, after drying and evaporating the solvent, 3.35 g. of an oil. This oil reacts with citric acid in alcoholic solution to give a colourless, crystalline citrate, m.p. 156—158°, or with methanolic picric acid solution to give a yellow picrate, m.p. 188—189°.

EXAMPLE 4

2(β-Phenethylaminoethoxy)4-methyl-t-butylbenzene.

32.5 g. of 2(β-toluene-p-sulphonyloxy-ethoxy) 4-methyl-t-butylbenzene and 65 ccs. of phenethylamine are heated at 95° for eight hours. The product is cooled, dissolved in water, treated with 80 ccs. of 40% sodium hydroxide solution and extracted with ether. The ether extract is shaken for a few minutes with approximately Normal hydrochloric acid, when the hydrochloride crystallises out. This is filtered and dried at 80—90° to obtain 27.4 g. of colourless needles, m.p. 174—175°. The free base obtained from this hydrochloride distils at 144—148°/0.5 mm., and may be converted to the same hydrochloride by warming with dilute hydrochloric acid.

EXAMPLE 5

2-(β-Phenethylaminoethoxy)4-methyl-t-butylbenzene isethionate.

A column of about 25 ccs. settled volume of "Deacidite F.F." anion exchange resin in the chloride form, is washed with a 1% aqueous solution of sodium isethionate until the washings give no reaction for chloride with silver nitrate solution. The column is then washed with methanol. A solution of 1.9 g. of 2-(β-phenethylaminoethoxy) 4-methyl-t-butylbenzene hydrochloride (obtained as described in Example 4) in 25 ccs. of methanol is run onto the column, which is eluted with about 100 ccs. of methanol. The eluate is evaporated to dryness and the residue recrystallised twice from a mixture of benzene and light-petroleum (b.p. 40—60°) to give 1.5 g. of colourless crystals, m.p. 102—103°. This isethionate salt is easily soluble in water.

EXAMPLE 6

2(2-t-Butyl-5-hydroxy-4-methylphenoxy) ethyl triethyl ammonium iodide.

A mixture of 1.4 g. of 2(β-diethylaminoethoxy) - 5 - hydroxy - 4 - methyl - t - butyl-

benzene and 6 ccs. of ethyl iodide, is boiled under reflux for 30 minutes and stood at room temperature overnight. The excess of ethyl iodide is distilled off and the residue is washed with ether and recrystallised twice from water to obtain 1.4 g. of white solid, m.p. 221° (dec.).

EXAMPLE 7

2(2-t-Butyl-4-methoxyphenoxy) ethyl trimethylammonium isethionate.

A solution of 2.5 g. of 2(2-t-butyl-4-methoxyphenoxy) ethyl trimethyl ammonium iodide in 30 ccs. of methanol is run onto a column of "Deacidite (Registered Trade Mark) FF" in the isethionate form as described in Example 5. The column is eluted with 100 ccs. of methanol and the eluate evaporated to dryness. The residue after recrystallisation from acetone/ether and from benzene afforded 1.65 g. of colourless, deliquescent plates, m.p. 102—104°.

EXAMPLE 8

2(β-N-piperidinoethoxy)-4-methyl-t-butylbenzene citrate.

A mixture of 3.6 g. of 2(β-toluene-p-sulphonyloxyethoxy) - 4 - methyl - t - butylbenzene and 10 ccs. of piperidine is heated on a boiling water bath for four hours. The unreacted piperidine is distilled from the water bath at reduced pressure and the residue dissolved in ether. The ether solution is washed with dilute sodium hydroxide solution and with water and is then extracted with two 50 cc. portions of approximately Normal hydrochloric acid. The acid extract is washed with ether, made alkaline with 40% sodium hydroxide solution, ether extracted and the ether washed with water, dried over magnesium sulphate and evaporated to dryness. The residual 1.9 g. of liquid base is reacted with 1.52 g. of citric acid in methanol solution to obtain 2.56 g. of white crystalline citrate, m.p. 156—158° (dec.), after recrystallisation from ethanol.

EXAMPLE 9

4-Acetamido-2-(β-diethylaminoethoxy) t-butylbenzene.

A mixture of 3.7 g. of 4-acetamido-2-hydroxy-t-butylbenzene, 70 ccs. of acetone, 3.15 g. of β-diethylaminoethylchloride hydrochloride and 10 g. of anhydrous potassium carbonate, is boiled under reflux for twenty-four hours. The inorganic residue is filtered off and the filtrate evaporated to dryness. The residue is dissolved in ether and extracted twice with approximately 2N. hydrochloric acid and once with water. The combined aqueous layers are made alkaline with sodium hydroxide solution and extracted with ether, which is washed with water, dried over magnesium sulphate and evaporated to an oil which crystallises on standing to give 3.3 g., m.p. 75—78°. Recrystallisation from n-hexane gives about 2 g. of product, m.p. 82—83°.

EXAMPLE 10

2(β-Diethylaminoethoxy)-4-hydroxy-t-butylbenzene.

A solution of 5.8 g. of 4-amino-2(β-diethylaminoethoxy)t-butylbenzene in 145 ccs. of approximately 2N. sulphuric acid, is stirred at about 0° and diazotised by addition of a solution of 1.45 g. of sodium nitrite in a small volume of water. The cooled diazonium salt solution is added, during fifteeen minutes, to a stirred solution of 11.6 g. of copper sulphate in 116 ccs. of 2N sulphuric acid at 80—90°. Stirring at 80—90° is continued until no more nitrogen is evolved, this being about one hour. The hot solution is saturated with hydrogen sulphide, filtered hot with suction and the residue washed with hot dilute sulphuric acid. The sulphate of 2(β-diethylaminoethoxy)4-hydroxy-t-butylbenzene which crystallises from the cooled filtrate, is filtered off and recrystallised from water to obtain 3.1 g., m.p. 173—174°. When a hot aqueous solution of this sulphate is treated with ammonia solution, 2.3 g. of 2(β-diethylaminoethoxy)4-hydroxy-t-butylbenzene is precipitated as a white solid, m.p. 102—103°. Recrystallisation from light-petroleum (b.p. 40—60°) gives a product, m.p. 106—107°.

The following List A of additional compounds may be prepared by one or more of the processes described in the above examples.

LIST A

2(β - Dimethylamino - α - methylethoxy)4-methyl - t - butylbenzene. b.p. 114—117/0.5 mm. Citrate, m.p. 153—154°. Picrate, m.p. 151—152°.

2(β - Dimethylaminoethoxy)4 - methyl - t-butylbenzene. b.p. 116—120/1 mm. Citrate, m.p. 163—164°. Picrate, m.p. 177—178°.

2(β - Diethylaminoethoxy)5 - methyl - t-butylbenzene, b.p. 125—128/1 mm. Citrate, m.p. 159—160° (dec).

2(β - Diethylaminoethoxy)1,5 - di - t-butylbenzene, b.p. 130—142/0.1 mm. Citrate, 166.5—167.5° (dec).

2(β - Diethylaminoethoxy)4 - methyl - 1,5 - di-t-butylbenzene, b.p. 193—198°/16 mm. Citrate, m.p. 163—164°. Picrate, m.p. 84—86°.

2(β - Diethylaminoethoxy)5 - methoxy-t-butylbenzene, b.p. 117—119/0.3 mm. Citrate monohydrate, m.p. 139—140° (dec).

2(β - Diethylaminoethoxy)5 - benzyloxy-t-butylbenzene, b.p. 184—187/0.3 mm. Citrate, m.p. 140—142° (dec).

5 - Acetamido - 2(β - diethylaminoethoxy) - 4-methyl-t-butylbenzene, m.p. 68—72°. Picrate, m.p. 189.5° (dec).

2(β - Phenethylaminoethoxy)4 - methyl-t-butylbenzene tartrate, m.p. 177—178°.

2(β - Diethylaminoethoxy)4 - hydroxy - t-butylbenzene citrate, m.p. 132—133°.

2(β - Diethylaminoethoxy) 4 - methoxy - t-butylbenzene citrate, m.p. 120—121°.

2(β - Diethylaminoethoxy)5 - hydroxy -

4-methyl-t-butylbenzene, m.p. 105—106°. Citrate, m.p. 112 (dec).

2(β - Diethylaminoethoxy)5 - methoxy - 4-methyl-t-butylbenzene citrate, m.p. 161.5° (dec).

2(2 - t - Butyl - 5 - methylphenoxy)ethyl ethyl dimethylammonium iodide, m.p. 174—175°; chloride, m.p. 190.5° (dec).

2(2 - t - Butyl - 5 - methylphenoxy)ethyl trimethylammonium iodide, m.p. 222—223°; chloride 189—190°; bromide, m.p. 205—206°; p-toluenesulphonate, 166—167°, salicylate, 154—155°; isethionate, 128.5—129.5°.

2(2 - t - Butyl - 4 - methoxyphenoxy)ethyl triethylammonium iodide, 180.5° (dec).

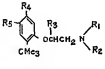
2(2 - t - Butyl - 4 - methoxy - 5 - methylphenoxy)ethyl triethylammonium iodide, m.p. 180° (dec).

2(2 - t - Butyl - 4 - hydroxy - 5 - methylphenoxy)ethyl triethylammonium iodide, 223° (dec); bromide, m.p. 190° (dec).

2(2 - t - Butyl - 4 - methoxyphenoxy)ethyl trimethylammonium iodidc, m.p. 198.5—199°.

WHAT WE CLAIM IS:—

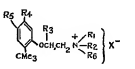
1. Basic ethers of o-tertiary butyl phenol of the following general structure:



where R_1 and R_2 may be the same or different groups chosen from hydrogen, an alkyl group of not more than four carbon atoms or phenethyl or R_1 and R_2 may be joined as part of a hetcrocyclic ring, e.g. piperidine; R_3 may be hydrogen or an alkyl group of not more than four carbon atoms, R_4 and R_5 may be hydrogen, an alkyl group of not more than four carbon atoms, alkyloxy, hydroxy, amino or acylamino groups.

2. Acid addition salts of the basic ethers described in Claim 1 formed from inorganic or organic acids, e.g., hydrochloric, tartaric, citric or isethionic acid.

3. Quatcrnary ammonium derivatives of the basic ethers of the following structure:



where R_1 and R_2 are alkyl groups of not more than four carbon atoms; R_3, R_4 and R_5 have the same significance as given in Claim 1 and R_6 is an alkyl group of not more than four carbon atoms; X is the anion associated with the quaternary salt and may be chloride, bromide, iodide, p-toluene sulphonate, salicylate or isethionate.

4. A compound selected from the group consisting of:

2(β - diethylaminoethoxy)4 - methyl - t-butylbenzene;

2(2 - t - Butyl - 5 - methylphenoxy)ethyl triethylammonium iodide;

2 - (2 - Aminoethoxy) - 4 - methyl - t-butylbenzene;

2(β - Phenethylaminoethoxy)4 - methyl - t-butylbenzene;

2 - (β - Phenethylaminoethoxy)4 - methyl - t-butylbenzene isethionate;

2(2 - t - Butyl - 5 - hydroxy - 4 - methylphenoxy) ethyl triethyl ammonium iodide;

2(2 - t - Butyl - 4 - methoxyphenoxy) ethyl trimethylammonium isethionate;

2(β - N - piperidinoethoxy) - 4 - methyl - t-butylbenzene citrate;

4 - Acetamido - 2 - (β - diethylaminoethoxy) t-butylbenzene;

2(β - Diethylaminoethoxy) - 4 - hydroxy - t-butylbenzene.

5. A compound selected from the groups referred to hereinbefore under the heading List "A."

6. A method of preparing any of the compounds claimed in the preceding claims substantially as hereinbefore described.

7. Basic ethers of o-tertiary butyl phenol and their quaternary ammonium derivatives, substantially as hereinbefore described.

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